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CROWELL & MORING LLP
Intellectual Property Group
P O Box 14300
Washington, DC 20044-4300

EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,414	SZYF ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-36,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The Response to the Office Action filled Sept. 22, 2003 is acknowledged. Amendments to the claims have been entered as requested. Claims 37 and 38 are cancelled; claims 32, 33 and 35 are amended; new claims 39-40 are added.

DETAILED ACTION

1. Objections

1.1. Claims

Newly submitted claim 39 and 40 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons.

The elected invention is Group XIII-2, which relates to the use of an antagonist or inhibitor of the human DNA demethylase of SEQ ID NO: 2, amino acids residues 150-411, for restoring an aberrant methylation pattern in the patient DNA. In response to the species election requirements Applicants elected the species of double stranded oligonucleotides and antisense oligonucleotides of DNA demethylase.

Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 39 and 40 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

1.2. Drawings

The replacement drawing sheets 1-50 are acknowledged. The figures are objected for the following reasons.

1. It is unknown to which enzyme, SEQ ID NO: 2 or 4, 6, and 8, an in case when it is relevant, to which cells, the data of Fig. 1-8, 10-16 are pertinent.
2. Fig. 8C illustrates the expression of dMTase in several tissues of unknown origin. Is this the expression of human enzyme (SEQ ID NO: 2, 4) in human tissues from a normal person? Is that expression of mouse enzyme (SEQ ID NO: 6, 8)?
3. Fig 10 B shows that imidazole increases efficiency of cytosine demethylation by dMTase of unknown SEQ ID NO, whereas applicants claim that imidazole is the dMTase inhibitor.
4. Fig. 11 is confusing because the volatilized methyl residues increase with imidazol concentration for DMTase, whereas their concentration should decrease because the imidazole inhibits the enzyme.
5. Description of Fig. 11C-11E is unclear. What does it mean: "transforms methylated cytosine to cytosine in a protein dependent manner"?
6. Fig. 14C is described as illustrating inhibition of tumorigenesis in vitro. The figure actually shows the inhibition of growth in soft agar colonies of tumor cells of unknown origin. The term tumorigenesis encompases many phenomena related to onset of cancerogenic transformation and progression of tumor, therefore the use the term is not proper.
7. Fig. 15, according to the description, illustrates inhibition of tumorigenesis in cell culture induced by expression of demethylase antisense vector. The figure

actually demonstrates the decrease in the colony formation by HEK293 cells transiently transfected with pRetro –antisense dMTase, wherein the dMTase is not identified.

2. Rejections

2.1. 35 USC section 101

Rejection of claim 38 is under 35 U.S.C. 101 made in the previous Office Action is moot because the claim has been cancelled.

2.2. 35 USC, section 112, second paragraph

Rejection of claim 32-38 is rejected under 35 U.S.C. 112, second paragraph, for reciting

(1) "restoring an aberrant methylation pattern", claim 32,

(2) "small molecule", claim 35.

Is withdrawn because the claims have been amended. The terms (1) and (2) are not defined by the claim or the specification.

Claim 36 recites the limitation "change of the methylation pattern" in the second line. There is insufficient antecedent basis for this limitation in the claim. The base claim recites the phrase "alteration of the methylation pattern".

Claim 35 is confusing, because the claim recites the phrase "an antisense oligonucleotide of DNA demethylase or an imidazole derivative thereof", which renders the claim indefinite. For examination purposes it is assumed that the proper phrase

should be "an antisense oligonucleotide of DNA demethylase or imidazole and derivatives thereof."

New rejection

Claim 32 and dependent claims 33-36 are rejected, because claim 32 recites the tem "a homologue thereof" that renders the claims indefinite absent the amino acid or DNA sequence encoding said homologue.

2.2. 35 USC, section 112, first paragraph

4.2.1. Lack of written description

Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for inhibiting tumorigenesis or altering methylation pattern in a patient DNA by any inhibitor of dMTase.

Applicants have failed to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

The term tumorigenesis is generic and encompases many phenomena related to onset of cancerogenic transformation and progression of tumor. Thus the claim is directed to a genus of methods directed to inhibition of many phenomena (species) of

tumorigenesis. It is unclear to which of this phenomena Applicants are referring to. Fig. 14 and 15 provide some data on inhibition of colony formation by tumor cells in soft agar. The feature of the colony formation is only one of many features of tumorigenesis, and the only species provided by applicants is not representative of all the other species.

The application is silent as to the methylation pattern of any gene in any patients and its alteration; this is a complete lack of written description.

Federal Circuit states that the primary function of the written description requirement is to insure that an inventor had possession of the claimed subject matter and to allow one skilled in the art to recognize what is claimed. *See in re Blaser*, 556F.2d 534, 194 U.S. P. Q. 122(CCPA 1977), *Enzo Biochem*, 285 F. 3d 1013, 62 U.S.P.Q.2d 1289. The written description requirement is satisfied by the disclosure of the claimed subject matter in such a descriptive means, *e.g.*, words, structures, figures and diagrams, to allow one skilled in the art to visualize or recognize the claimed subject matter, *Enzo Biochem*. 285 F. 3d 1013."

One skilled in the art is not able to visualize or recognize the invention because the claimed subject matter is not disclosed in such descriptive means as words, figures or diagrams presenting the recited biological phenomena and their changes. Given this lack of written description of tumorigenesis phenomenon to be inhibited, and of alteration of any methylation pattern in a patient by use of inhibitor of DNA demethylase one skilled in the art is not convinced that inventors had possession of the claimed invention at the time the application was filed.

In addition, the method of claim 32 uses any antagonist or inhibitor of DNA demethylase. The terms antagonist or inhibitor are generic terms the scopes of which cover large and variable chemical compounds. The Applicants teach only following representatives of the claimed genus: oligonucleotide consisting of 4 units C^mG, wherein these four units may be repeated several times, anti-DNA demethylase antibody, an antisense oligonucleotide of DNA demethylase and imidazol. In addition, the structure of the antisense oligonucleotide of DNA demethylase is not described in details, because the antisense vector of Fig. 15 is depicted schematically. This description is insufficient to give the identifying characteristics of all inhibitors as broadly recited by the claim. Given the lack of structural characteristics of additional representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

In traversing this rejection, Applicants in their Remarks write on page 8, line 22:

> "As specifically noted by the examiner, the specification teaches a variety of different antagonists and inhibitors; oligonucleotides consisting of 4 units of C^mG, anti -DNA demethylase antibody, antisense oligonucleotide of DNA demethylase and chemicals such as imidazole. Such variety of different compounds, taught as antagonists and inhibitors in the specification, teach that

antagonists and inhibitors of DNA demethylase can cover a large range of different structure and fields of compounds. Thus, it would be unfair to the Applicants to limit the claim with more non-generic terminology."

Applicants' arguments have been fully considered but are found not persuasive. Rejection of claims for lack of written description and limitation of the language of the claim to overcome the rejection is not the question of fairness or unfairness. When the language is generic, i.e., the scope of the claim encompasses any inhibitor including the one disclosed by someone else, or an unknown inhibitor, the claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Rejection

Claim 32 and dependent claims 33-36 are rejected because they are generic for the term homologue of human dMTAse of SEQ ID NO: 2. The claims are directed to a genus of methods using a large genus of homologs of said human enzyme. The scope of the claim encompasses the use of any homolog of human DNA demethylase from any eukaryotic cells or man-made. Applicants present only three species of homologs of SEQ ID O: 2, which are SEQ ID NO: 4, 6, and 8. This is, however, not enough to provide someone skilled in the art with identifying characteristics of the genus. In addition, the specification is confusing in its teaching as to which homologs of SEQ ID

NO: 2, or SEQ ID NO: 2 itself, have any effect on phenomena involved in tumorigenesis and have any effect on methylation of DNA in any cell or tissue. Thus, one skilled in the art is not convinced that Applicants were in possession of the claimed invention when the application was filed.

Claim 36 is rejected because the claim is directed to a method of inhibition of tumorigenesis and alterating metylation of pattern in a patient DNA, wherein the alteration of the pattern activates a silent gene. Applicants' attention is turning to the fact that activation of a silent gene can have actually an opposite effect than that intended by applicants. For example activation of an oncogene is one of phenomena involved in tumorigenesis, and not in inhibiting it. Thus, because the Applicants did not described any gene whose activation by demethylation is related to inhibition of tumorigenesis, the one skilled in the art is not convinced Applicants were in possession of the claimed invention when the application was filed

2.2.2. Scope of enablement

Claim 32-38 were rejected in the previous Office Action for lack of enablement. Rejection of claims 37-38 is moot because the claims have been cancelled.

The amended claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of colony formation of tumor cells <u>in vitro</u> by some inhibitors of dMTAse, does not reasonably provide

enablement for inhibition of tumorigenesis in any patients. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 32 is directed to a method for inhibition of tumorigenesis in a patients using any inhibitor of dMTAse, the specification, however, fails to teach inhibition of any other phenomena related to tumorigenesis than the ability of colony formation by tumor HEK 293 cells *in vitro* (Fig. 15) or unknown cells (Fig. 14) in soft agar *in vitro.* Applicants fail to describe any other phenomena of tumorigenesis related any type of tumor and patient as well as inhibition of the grow by any other inhibitor, see the above rejection for lack of written description. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses inhibition, of any phenomenon related to tumorigenesis of any type of tumor in any patients.

The one skilled in the art realizes that mechanisms underlying tumorigenesis are versatile and not every tumorigenesis is caused by demethylation of cytosine in GC islands, which may lead to derepression of some genes involved in carcinogenesis (oncogenes). The example of the mechanism of tumorigenesis not related to methylation or demethylation of the patient's DNA is deletion or mutation in one of tumor suppressor genes. Therefore, one who would like to use demethylase inhibitors to treat tumorigenesis has to measure the level of the enzyme for all possible tumors at many steps of tumor development and aspects of tumorigenesis, in many patients, and select as candidates for treatment only those types of tumors where production of DNA demethylase is increased in comparison with that of healthy patients.

In conclusion, without further guidance on the part of Applicants as to the details regarding phenomenon involved in tumorigenesis of a definite type of tumor experimentation left to those skilled in the art has a low probability of success and is improperly extensive and undue.

Dependent claims 33-36 are included in this rejection because they do not correct the language of the base claim.

In response to this rejection Applicants write:

"As discussed above, claim 32 has been amended to be directed to a method of inhibition of tumorigenesis and for altering a methylation pattern in a patient DNA. Support

for this amendment can be found on page 10, lines 19-23, Fig.14C, Fig.15 and page 32, line 26 to page 33, line 5 of the specification."

The fragments of the specification on page 10, lines 19-23 read as follows:

"Fig. 14C illustrates inhibition of tumorigenesis *in vitro* by an inhibition of demethylase;

Fig. 15 illustrates inhibition of tumorigenesis in cell culture by induced expression of demethylase antisense vector."

Fig. 14C is described as illustrating inhibition of tumorigenesis in vitro. The figure actually shows the decrease in colony formation in soft agar by tumor cells of unknown origin, (What was the tumor, who was the patient?), by the dMTase inhibitor meCpG. In addition, it is unknown which demethylase was inhibited in the experiment of Fig. 14. Fig. 15 demonstrates the decrease in colony formation by HEK293 cells transiently transfected with pRetro –antisense dMTase, wherein the dMTase, tumor cells and a patient are not identified. Neither of these figures show inhibition of tumorigenesis, which encompasses many phenomena at the cellular and systemic level that are related to the onset of tumorigenesis and its progression. Thus, the quoted passage of the specification does not provide sufficient teachings and guidance to make and use the invention as claimed.

In addition, claim 32 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition by meCpG, antisense dMTAse DNA, imidasol and its derivatives, and dMTAse antibodies, does not reasonably provide enablement for inhibition by any known and unknown inhibitor of dMTAse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses inhibition by any inhibitor of dMTAse, of any phenomenon related to tumorigenesis in any type of tumor in any patients.

The state of art of inhibiting tumorigenicity by inhibitors of dMTASE is in early stage, therefore predicatability or unpredicatability in the art is high. The claim is

directed to the use of any known and unknown inhibitor of dMTAse in a patient. However the in vitro inhibitors disclosed by Applicants are not representative species of the genus of dMTAse inhibitors which certainly include chemical compounds of different structure whose metabolism and toxicity in patients' body are unknown. Although the enablement is not precluded by screening many chemical agents, when the number of potential inhibitors is large the Applicants should provide sufficient guidance regarding their chemical structure. Without such guidance experimentation left to those skilled in the art has a low probability of success and is improperly extensive and undue.

2.2.3. Lack of enablement

Amended claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 32 is directed to a method for altering methylation pattern in a patient DNA, the specification, however, fails to teach what is methylation pattern in a patient and how to alter it. Thus, to make and use the claimed invention necessitates undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art,

(f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses alteration DNA methylation pattern in any patient. However, Applicant do not provide any teaching of what a pattern is or how to alter the methylation pattern. There is no guidance as to who is going to be the patient nor what is the tissue from which the DNA is to be extracted or how to visualize the pattern of DNA methylation. Applicants only provide the guidance how to measure the overall demethylase activity but not the pattern of DNA metylation. There is no a single measurement of percentage of cytosine methylation for any single gene. Those skilled in the art know that the pattern of DNA methylation is different in different genes, depending on the nucleotide sequence and the state of cell differentiation or its physiological state.

In conclusion, without further guidance on the part of Applicants as to the details regarding the measurement and visualization of methylation pattern and required alteration in the methylation pattern, experimentation left to those skilled in the art has a low probability of success and is improperly extensive and undue.

Dependent claims 33-36 are included in this rejection because they do not correct the language of the base claim.

In response to this rejection Applicants write:

"As discussed above, claim 32 has been amended to be directed to a method of inhibition of tumorigenesis and for altering a methylation pattern in a patient DNA. Support for

this amendment can be found on page 10, lines 19-23, Fig.14C, Fig.15 and page 32, line 26 to page 33, line 5 of the specification [emphasis added]. In addition, claim 37 and 38 have been cancelled. The applicants submit, therefore, that one skilled in the art would be able to make/or use the invention."

Applicants' argument has been fully considered but is found not persuasive for the following reasons. The fragment of the specification on page 32, line 26 to page 33, line 5 reads as follows:

"The Km of DNA dMTAse for hemimetylated and fully methylated DNA was determined by measuring the initial velocity of the reaction at different concentration of substrate (Table 2). The calculated Km for hemimethylated DNA is 6 nM which is two fold higher than the Km for DNA methylated on both strands, 2.5-3 nM, (Table 2). It is unclear yet whether this small difference in affinity to the substrate has any significance in a cellular context. Thus similar to DNA MetAse DNA dMTAse shows dinucleotide sequence selectivity but in difference from DNA MeTase which shows preferency to hemimethylated substrates dMTAse prefers fully methylated DNA which is consistent with a role for DNA dMTAse in altering established methylation patterns."

The passage characterizes specificity of the enzyme for its substrate, which is a fully methylated DNA. The passage does not teach any established pattern of

methylation for any gene or DNA molecule from any patient, and the specification does not teach any changes or alterations in the methylation pattern of such a molecule.

5. Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

Art Unit 1652

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600